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Original article

Clinical and genetic risk factors for asthma exacerbations and mortality in adults

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Abstract: *Background* — According to epidemiological studies, nearly 7 million people in Russia suffer from bronchial asthma (BA), of which 1 million have a severe form of the disease that is difficult to control. Insufficiently effective control of BA leads to a reduction in the quality of life, the development of its more severe forms, an increase in the frequency of exacerbations of the disease, and an increase in the number of disability and death cases in patients.
Objective — The goal of our research was conducting a long-term cohort study of BA in adults living in the Republic of Bashkortostan and assessing the clinical and prognostic value of internal and external risk factors for exacerbation and death from BA.
Methods and Results — We analyzed the medical records of 213 BA patients 18 to 67 years a age from 2012 through 2022. Genotyping of six SNPs in *ADRB2* (rs1042713, rs1042714), *CRHR1* (rs242939, rs1876828), *NR3C1* (rs41423247), and *HRH3* (rs3787429) genes was performed by real-time polymerase chain reaction. Using regression analysis, we assessed predictors of the risks of exacerbation and death in BA and built multivariate models for each outcome.
Conclusion — As a result of regression analysis, significant clinical and prognostic risk factors for re-exacerbation and death from BA were identified.

Keywords: bronchial asthma, gene, mortality, exacerbation.

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Introduction

Bronchial asthma (BA) is a chronic respiratory disease with recurrent exacerbations that have a negative impact on the quality of life, which makes it a socioeconomic problem rather than just a medical issue [1, 2]. The total number of patients with BA exceeds 300 million worldwide. In Russia, according to epidemiological studies, about 7 million people suffer from it, of which 1 million have a severe form of the disease that is difficult to control. The World Health Organization estimates that each year BA causes the loss of 15 million disability-adjusted life years (DALYs constitute a measure that combines years of life lost due to premature death with years of healthy life lost due to disability), which represents 1% of the total global burden of disease [1, 2, 3].

Factors that influence the risk of developing BA can be divided into factors that cause the disease to develop and factors that trigger its symptoms. The first group includes internal factors (primarily genetic), while the second usually involves external factors. However, the mechanisms of effect of these factors on the development and manifestations of BA are complex and interdependent. For example, susceptibility to BA is likely determined both by the interaction of genes with each other and by their interaction with external factors [4]. According to the published data, the heritability of BA ranges from 55 to 74% in adults and reaches 90% in children. The most statistically significant associations, repeatedly confirmed in studies performed by different authors on different population samples, showed polymorphic variants of genes located in the regions 17q12-21, 6p21.32, 9p24.1, 2q12, and 5q22.1 [5, 6].

Currently, the main goal of BA therapy is to achieve complete control and high quality of life in all patients, regardless of the severity of the disease. Insufficiently effective control of BA leads to a reduction in the quality of life, the development of its more severe forms, an increase in the frequency of exacerbations of the disease, as well as an increase in the number of disability and mortality cases in BA patients [7]. Numerous data of clinical trials and nationwide cross-sectional studies has identified risk factors for exacerbations and mortality in people with BA. Crucial factors of the kind include age, smoking, poor asthma control, reduced lung function, and lack of follow-up. However, cohort studies of risk factors for BA mortality are rare. There is little research on the long-term consequences of asthma-related exacerbations and mortality [8].

The goal of our research was conducting a long-term cohort study of BA in adults living in the Republic of Bashkortostan and

assessing the clinical and prognostic significance of internal and external risk factors for exacerbation and death in asthma.

Material and Methods

Patients

During our research, we analyzed the medical histories of 213 patients diagnosed with BA aged 18–67 years (122 women and 91 men) who underwent inpatient treatment in the Division of Allergy in the City Clinical Hospital No. 21 of Ufa, Republic of Bashkortostan, from 2012 to 2022. It should be noted that we excluded repeated hospitalizations and patients referred by military registration and enlistment offices for clarification of the diagnosis. As a result of clinical, laboratory and instrumental examination, the diagnosis of BA was confirmed in all patients. External respiration function was assessed using a computer spirograph (Erich Jaeger, Germany) via analyzing the flow-volume loop. All patients with BA gave informed consent to participate in the study. The study protocol was approved by the Bioethics Committee of the Institute of Biochemistry and Genetics at Ufa Federal Research Center of the Russian Academy of Sciences (protocol No. 7 of February 10, 2011). DNA samples from these patients were isolated as material for the study.

Treatment of BA exacerbations was carried out in accordance with the recommendations of the Global Initiative for Asthma (GINA, 2009-2022). Patients were treated with conventional therapy of anti-inflammatory nature and medicinal drugs on demand taken to relieve symptoms of the disease; depending on the severity of the exacerbation, courses of systemic corticosteroids were prescribed. When studying the medical records of our patients for the period from 2012 to 2022, cases of repeated exacerbations and 22 deaths of patients from BA were identified. Clinical characteristics of the patients are presented in *Table* 1.

Genotyping of DNA samples

Total genomic DNA was isolated from 5 mL of venous blood using standard phenol-chloroform extraction. Genotyping of six SNPs in *ADRB2* [rs1042713 (p.Gly16Arg, c.46G>A), rs1042714 (p.Gln27Glu, c.79C>G)], *CRHR1* [rs242939 (c.241+1631A>G), rs1876828 (c.1107+111C>T)], *NR3C1* [rs41423247 (p.1184+646C>G)], and *HRH3* rs3787429 (g.62216348C>T) genes was performed by real-time polymerase chain reaction (PCR) using TaqMan technology on the platform of the CFX96 device (Biorad Touch Real-Time PCR Detection System).

Table 1. Clinical characteristics of the studied asthma patients

Characteristics	*Counts (%) or Mean (range)*
Age, years	52 (36-66)
Men, number (%)	91 (42.7%)
Women, number (%)	122 (57.3 %)
Total serum IgE level (IU/mL)	146.6 (57.0-314.3)
Age at asthma onset, years	38 (23-48)
FEV1 (%)	72.0 (62.0-84.0)
VC (%)	83.5 (77.3-88.8)
Allergic asthma phenotype, number (%)	38 (15.0%)
Nonallergic asthma phenotype, number (%)	78 (36.6%)

FEV1, forced expiratory volume in one second; VC, vital capacity of the lungs.

Table 2. Results of logistic regression analysis for each gene for the *exacerbation* event in asthma

Gene/Genotypes	*Estimate*	*Standard error*	*P-value*
ADRB2 rs1042713 (p.Gly16Arg, c.46G>A)			
Intercept	-1.0986	0.3482	0.0016**
ADRB2 rs1042713*GA	0.5645	0.4097	0.1682
ADRB2 rs1042713*GG	-0.3083	0.4743	0.5157
ADRB2 rs1042714 (p.Gln27Glu, c.79C>G)			
Intercept	-0.9445	0.2572	<0.001***
ADRB2 rs1042714*CG	0.2041	0.3373	0.5452
ADRB2 rs1042714*GG	-0.4906	0.5601	0.3811
CRHR1 rs242939 (c.241+1631A>G)			
Intercept	-0.9040	0.1693	<0.001***
CRHR1 rs242939*AG	0.1418	0.4881	0.771
CRHR1 rs242939*GG	-0.4823	1.1308	0.670
CRHR1 rs1876828 (c.1107+111C>T)			
Intercept	-0.8157	0.1771	<0.001***
CRHR1 1876828*CT	-0.4652	0.3989	0.244
CRHR1 1876828*TT	15.3818	882.7434	0.986
NR3C1 rs41423247 (c.1184+646C>G)			
Intercept	-0.8995	0.2421	<0.001***
NR3C1 rs41423247*CG	0.0364	0.3336	0.9130
NR3C1 rs41423247*GG	-0.1419	0.5330	0.7899
HRH3 rs3787429 (g.62216348C>T)			
Intercept	-1.0664	0.2530	<0.001***
HRH3 rs3787429*TC	0.5963	0.3438	0.0828
HRH3 rs3787429*TT	-0.5759	0.5128	0.2614

*, **, *** Statistical significance of the coefficients at p<0.05, p<0.01 and p<0.001, respectively.

Table 3. Results of logistic regression analysis for each gene for the *death* event in asthma

Gene/Genotypes	*Estimate*	*Standard error*	*P-value*
ADRB2 rs1042713 (p.Gly16Arg, c.46G>A)			
Intercept	-2.3026	0.5244	<0.001***
ADRB2 rs1042713*GA	-0.5539	0.6975	0.427
ADRB2 rs1042713*GG	0.6733	0.6282	0.284
ADRB2 rs1042714 (p.Gln27Glu, c.79C>G)			
Intercept	-1.8718	0.3397	<0.001***
ADRB2 rs1042714*CG	-0.8362	0.5414	0.122
ADRB2 rs1042714*GG	-0.1651	0.7016	0.814
CRHR1 rs242939 (c.241+1631A>G)			
Intercept	-2.1335	0.2493	<0.001***
CRHR1 rs242939*AG	-0.9110	1.0534	0.387
CRHR1 rs242939*GG	-14.4326	1073.1091	0.989
CRHR1 rs1876828 (c.1107+111C>T)			
Intercept	-2.1972	0.2722	<0.001***
CRHR1 1876828*CT	-0.1542	0.5898	0.794
CRHR1 1876828*TT	-13.3688	1455.3976	0.993
NR3C1 rs41423247 (c.1184+646C>G)			
Intercept	-2.3848	0.3950	<0.001***
NR3C1 rs41423247*CG	-0.1001	0.5575	0.8575
NR3C1 rs41423247*GG	1.1039	0.6415	0.0853
HRH3 rs3787429 (g.62216348C>T)			
Intercept	-1.8648	0.3240	<0.001***
HRH3 rs3787429*TC	1.0530	0.6070	0.0828
HRH3 rs3787429*TT	-0.2454	0.6207	0.6926

*, **, *** Statistical significance of the coefficients at p<0.05, p<0.01 and p<0.001, respectively.

Table 4. Estimates of coefficients in a multivariate model of the *exacerbation* event in asthma

Factor	*Estimate± Standard error*	*P-value*
Intercept	-1.259±1.086	0.246
Female	0.535±0.379	0.158
Employee	1.374±0.688	0.045*
Private sector	0.350±1.162	0.763
Manager	-14.637±1238.41	0.991
Unemployed	0.922±0.721	0.201
Retired	0.110±0.665	0.869
Student	-0.114±0.833	0.987
Season of exacerbation: spring	-1.557±0.717	0.030*
Season of exacerbation: summer	-1.413±0.898	0.115
Season of exacerbation: fall	-0.839±0.687	0.223
First manifestation of BOS: 5-10 years ago	1.566±0.596	0.008**
First manifestation of BOS: 10-20 years ago	1.357±0.555	0.014*
First manifestation of BOS: more than 20 years ago	1.299±0.576	0.024*
First manifestation of BOS: at the time of the study	0.337±0.597	0.735
Not taking IGCS	-0.044±0.419	0.916
Not taking Symbicort	-0.559±0.442	0.205
Not taking Berodual	-0.408±0.352	0.246
IgE<100 IU/mL	0.459±0.352	0.192

BOS, bronchiolitis obliterans syndrome; IGCs, inhaled glucocorticoids; *, ** The coefficient is statistically significant at p<0.05 or p<0.01, respectively.

Table 5. Estimates of coefficients in a multivariate model of the *death* event in asthma

Factor	*Estimate± Standard error*	*P-value*
Intercept	-0.584±1.548	0.706
Age	0.039±0.019	0.044*
No GCs taken regularly	-1.323±0.586	0.024*
FEV1	-0.054±0.017	0.0013**

GCs, glucocorticoids; *, ** the coefficient is statistically significant at p<0.05 or p<0.01, respectively.

Statistical data processing

Clinical and biochemical features of the study patients were presented as Me (IQR), where Me is the median and IQR is the interquartile range between the values of the 25th and 75th percentiles. All SNPs were tested for deviation from Hardy-Weinberg equilibrium (HWE) in the HWE study group (χ2).

To identify predictors of the risks of exacerbation and death in BA, data of 213 patients were analyzed. We employed a binary choice regression model with a logistic distribution (hereinafter referred to as the logistic regression model) as a tool for classifying a factor as a risk factor for death or exacerbation. In the general case, the logistic regression model has the form:

$$P(y_i=1) = \Lambda(b_1 \bullet x_1 + b_2 \bullet x_2 + \ldots + b_k \bullet x_k + b_0) = \Lambda(x^{Tb}),$$

where y_i=1 is the target event in two versions of the model (death/survival and exacerbation/no exacerbation); $X=(x_1, x_2, \ldots, x_k)$ are independent variables (risk factors), $B=(b_1, b_2, \ldots, b_k)$ is the vector of model coefficients, T is the sign of a transposition, Λ is the logistic distribution function. The model describes that a particular risk predictor increases or decreases the probability of death (exacerbation) in patients with BA.

Identification of risk predictors was carried out using a statistical modeling environment in two stages. At the first stage, sets of logistic models (with only one influencing factor) were built for two outcome options separately: for the risk of death and for the risk of exacerbations. It should be noted that in the case of risk predictors in the form of a factor variable with several levels (for example, season when exacerbation occurs), all levels of this variable were taken into account in the model as dummy variables. For such models, we determined the coefficient for the effect variable, the standard error of the coefficient, and the corresponding *p*-level. This *p*-level value was calculated to test the null hypothesis that the coefficient of the factor variable is equal to zero, i.e., in fact, that there is no effect of the factor on the risk of death or exacerbation of the disease. If $p<0.05$, then the null hypothesis was rejected and the factor was considered a true predictor of the risk of an adverse event. These models were interpreted solely from the standpoint of choosing the influencing factor for a multimarker model: only factors that individually influenced the probability of an outcome were taken into the model, $p<0.05$.

At the second stage, multivariate models were built for each outcome, that is, models that took into account several factors influencing the risk of exacerbation or the risk of death. For such models, we determined the coefficient for the effect variable, the standard error of the coefficient, and the corresponding *p*-level. A factor was assumed to have an effect if its coefficient was estimated at $p<0.05$. Statistical data processing was performed using Microsoft Excel 2019 and R programming language (version 4.2.2).

Results

Our research involved a longitudinal study of BA, during which genetic predisposition was examined in combination with climatic, environmental and other factors influencing the development of BA in adults in the Republic of Bashkortostan. An analysis of the medical records of patients undergoing hospital treatment was carried out, and the dynamics of morbidity and mortality over a ten-year period was investigated. Predictors of the risk of exacerbation and death from BA were assessed, and multivariate models were built for each outcome; i.e., models that took into account several factors influencing the risk of exacerbation or the risk of death in this disease.

We genotyped six SNPs in the *ADRB2* (rs1042713, rs1042714), *CRHR1* (rs242939, rs1876828), *NR3C1* (rs41423247), and *HRH3* (rs3787429) genes in patients with BA. The distribution of genotype frequencies of polymorphic gene variants was tested for HWE, and minor allele frequency (MAF) was assessed in the entire study group. The following results were obtained for patients: *ADRB2* rs1042713 (p=0.71, A allele frequency was 45.5%); *ADRB2* rs1042714 (p=0.41, G allele frequency was37.5%); *CRHR1* rs242939 (p=0.00002, G allele frequency was 9.24%); *CRHR1* rs1876828 (p=0.13, T allele frequency was 12.26%); *NR3C1* rs41423247 (p=0.70, G allele frequency was 34.6%); and *HRH3* rs3787429 (p=0.05, T allele frequency was 39.0%).

Using logistic regression, the studied polymorphic gene variants *ADRB2*, *CRHR1*, *NR3C1*, and *HRH3* were assessed as predictors of the risk of exacerbations and the risk of death in patients with BA (*Tables 2* and 3).

The obtained results implied that the presence of the rs3787429*TC genotype in the *HRH3* gene increased the likelihood of repeated exacerbation of BA (p=0.08). The patient's genotype rs3787429*TC in the *HRH3* gene and the genotype

rs41423247*GG in the *NR3C1* gene (p=0.08) increased the likelihood of death from BA (*Table* 3). The intercept in the constructed models was statistically significant at p<0.05, which did not exclude the possible influence of any other factors on the risk of exacerbation and death in BA.

The analysis of the clinical and demographic characteristics of patients with BA showed that the following factors were statistically significant (p<0.05) as predictors of univariate regression models of the *BA exacerbation* event: female gender, occupation (employee), season of exacerbation (spring), early age at first manifestations of bronchiolitis obliterans syndrome (BOS) (5-10 years ago, 10-20 years ago and more than 20 years ago), absence of inhaled glucocorticoids (IGCs), taking Berodual and Symbicort, and IgE<100 IU/mL.

Similar analysis of the univariate regression models for the *death* event, the following factors were statistically significant (p<0.05): patient age, lack of regular intake of corticosteroids, and changes in spirography parameters (FEV1).

An analysis of multicomponent models was performed, taking into account a number of factors influencing the risk of exacerbation or the risk of death in BA. *Table* 4 presents the results of assessing the multivariate model. As can be seen, the following factors are statistically significant for the *exacerbation* event: occupation (employee), season spring), manifestation of BOS 5-10 years ago, 10-20 years ago and more than 20 years ago.

Table 5 presents the results of assessing the multivariate model of the patient's *death* event; statistically significant factors (p<0.05) were as follows: patient age, lack of regular use of corticosteroids, and changes in spirography parameters (FEV1).

Discussion

According to the provisions of the Global Strategy for Asthma Management and Prevention, the goal of its therapy is maintaining clinical control of the disease rather than just achieving the control. Exacerbation of BA can be caused by various triggers that induce inflammation of the airways or provoke acute bronchospasm. These triggers can vary significantly from patient to patient [2]. Hereditary factors make a significant contribution to the occurrence of BA. It is now generally accepted that the genetic basis of asthma is a combination of hereditary predisposition to the development of atopy and bronchial hyperresponsiveness. Each of these genetic factors significantly increases the risk of the disease. The presence of certain genetic combinations, as well as the influence of external factors, determine the characteristics of the clinical phenotype [5].

Our research was carried out as an observational study of patients with BA treated at the City Clinical Hospital No. 21 of Ufa, Bashkortostan, Russia, over a ten-year period (2012-2022). To assess the clinical and prognostic significance of intrinsic and extrinsic risk factors for exacerbation and death in BA, univariate and multivariate models were analyzed via logistic regression.

The studied polymorphic variants of *ADRB2, CRHR1, NR3C1,* and *HRH3* genes were assessed as predictors of the risk of exacerbations and the risk of death in patients with BA. We discovered that the presence of the rs3787429*TC genotype in the *HRH3* gene increased the likelihood of BA re-exacerbation, while the presence of the rs3787429*TC genotype in the *HRH3* gene and rs41423247*GG genotype in the *NR3C1* gene increased the likelihood of death in BA. According to published data, the polymorphic locus rs41423247C>G of the *NR3C1* gene was linked to alternative splicing of mRNA [9]; while the rs41423247*G allele of the *NR3C1* gene was associated with severe BA in patients from Ukraine [10], with high levels of IgE in children from Russia [11], and with an increase in the number of cases of exacerbations and severe BA in Egyptian children [12]. Thangam et al. established that *HRH3* gene (20q13.33) knockout led to a more severe course of neuroinflammatory diseases and increased the expression of IFNγ-inducible protein 10 (IP-10) and chemokines (MIP-2, CXCR3) in T cells; hence, they assumed that *HRH3* is involved in functioning of the blood-brain barrier [13]. A study of 95 polymorphic variants in patients from Australia, Netherlands and Denmark revealed an association of rs6062144 (located in the intergenic region near the *HRH3* gene) with the development of BA [14].

The multivariate model associated with the risk of exacerbations of BA included the following factors: occupation (employee), season (spring), age of BOS manifestation (5-10 years ago, 10-20 years ago, and more than 20 years ago). Of the examined significant factors associated with the risk of BA exacerbation, the spring period was identified, which was consistent with a finding of a cohort study in Netherlands that the risk of severe BA exacerbations was highest in spring and fall. Peaks observed in spring may be due to exposure to tree pollen and other aeroallergens (e.g., birch, elm, and alder pollen, etc.) [15]. Early onset of BOS is a factor increasing the risk of future BA exacerbations. Long-term obstruction of the bronchi leads to an increase in airway resistance, a reduction in the forced expiratory volume (FEV1) and peak expiratory flow rate, and also the need for auxiliary muscles to participate in the act of breathing [16].

A multivariate model that included factors, such as patient age, lack of regular use of corticosteroids, and changes in spirography (FEV1), was associated with the risk of death from BA. The presence of a factor associated with the risk of death in the tested model, such as the patient age, is in good agreement with findings that BA in adults had a worse prognosis and suboptimal response to treatment, compared with children [17]. Longer disease duration in adults is associated with ongoing inflammation and subsequent airway remodeling, which in turn leads to poor outcomes [18]. Of particular importance is the monitoring of inflammatory and pathophysiological features rather than the clinical manifestations of BA alone. Reducing inflammation with basic therapy (inhaled corticosteroids) was shown to contribute to achieving good clinical control and reducing the risk of exacerbations, as well as non-adherence to BA treatment and lack of good control of the disease was demonstrated to represent a risk of death [19, 20]. Airflow obstruction measurement is a strong predictor of mortality in patients with BA as well. Objective measures of pulmonary function (such as FEV1) are useful predictors of hospitalization in these patients [21, 22]. Poor BA control, including extensive use of short-acting β2-agonists, predicted long-term exacerbations and mortality over 30 years in Danish patients with BA. Improving BA control, including pulmonary function, and reducing the use of short-acting bronchodilators is vital for a better long-term prognosis of BA [8].

Hence, as a result of regression analysis, significant clinical and prognostic risk factors for re-exacerbation and death from BA were identified. Multivariate models did not reveal a significant effect of genetic factors on the risk of exacerbation and death. Understanding the risk factors for exacerbations in patients with BA will allow developing more effective measures for achieving

control of this disease. Knowledge of the risk factors for asthma-related mortality is critical for customized treatment planning for this disease and, consequently, for reducing associated morbidity and mortality.

Conclusion

To assess the clinical and prognostic significance of intrinsic and extrinsic risk factors for exacerbation and death in BA, univariate and multivariate models were analyzed via logistic regression. Multivariate models did not reveal a significant influence of genetic factors on the risk of exacerbation and death. Significant clinical and prognostic risk factors for re-exacerbation of BA have been identified. A multivariate model that included several (patient age, lack of regular corticosteroid use, and changes in spirography) was associated with the risk of death from BA. Knowledge of the risk factors for asthma-related mortality is critical for planning and providing customized treatment for the disease, and therefore it may reduce the associated mortality.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Research Bioethics Committee of the Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences. and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare no conflicts of interest.

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